



REFERENCE CBBB

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF PENNSYLVANIA

SMITHKLINE BEECHAM CORPORATION and
BEECHAM GROUP, P.L.C.

v.

CIVIL ACTION
NO. 99-CV-2926
NO. 00-CV-5953

GENEVA PHARMACEUTICALS, INC.

SMITHKLINE BEECHAM CORPORATION,
SMITHKLINE BEECHAM P.L.C. and
BEECHAM GROUP, P.L.C.

v.

CIVIL ACTION
NO. 99-CV-4304
NO. 00-CV-4888
NO. 01-CV-159
NO. 01-CV-2169

APOTEX CORPORATION, APOTEX, INC.
and TORPHARM, INC.

Judge Richard Barclay
Surrick

SMITHKLINE BEECHAM CORPORATION,
SMITHKLINE BEECHAM, P.L.C. and
BEECHAM GROUP, P.L.C.

v.

CIVIL ACTION
NO. 00-CV-1393
NO. 00-CV-6464
NO. 01-CV-2602

ZENITH GOLDLINE
PHARMACEUTICALS, INC.

SMITHKLINE BEECHAM CORPORATION and
BEECHAM GROUP, P.L.C.

v.

CIVIL ACTION
NO. 01-CV-1027
NO. 01-CV-3364

ALPHAPHARM PTY, LTD.

SMITHKLINE BEECHAM CORPORATION and
BEECHAM GROUP, P.L.C.

v.

CIVIL ACTION
NO. 01-CV-2981

ANDRX PHARMACEUTICALS, INC.,
ANDRX PHARMACEUTICALS, L.L.C.
and BASF CORPORATION

SMITHKLINE BEECHAM CORPORATION and
BEECHAM GROUP, P.L.C.

v.

CIVIL ACTION
NO. 01-CV-5770

ENDO PHARMACEUTICALS, INC.

AFFIDAVIT OF DR. ROBIN ROMAN IN SUPPORT OF SMITHKLINE BEECHAM
CORPORATION AND SMITHKLINE BEECHAM, P.L.C.'S OPPOSITION TO
TORPHARM'S MOTION FOR SUMMARY JUDGMENT OF INVALIDITY OF
CLAIMS 1 AND 2 OF U.S. PATENT NO. 6,113,944

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Affidavit of Dr. Robin Roman

I, Dr. Robin Roman, an employee of Plaintiff GlaxoSmithKline, formerly, SmithKline Beecham Corporation, SmithKline Beecham Corporation and SmithKline Beecham p.l.c., (collectively "SB"), declare as follows:

1. My curriculum vitae (a copy of which is attached as Ex. A), shows my educational background and employment history. I have been an employee of SB for over eighteen years. I joined SB in 1983 as Associate Director of Preformulation, Analytical Methodology and Stability Testing at SB's Upper Merion site in the U.S. In 1987, I became the Associate Director of Liquid Formulations and Macromolecule Development at Upper Merion. From 1989 to 1991, I was Director of Pharmaceutical Research at Upper Merion where I directed formulation activities to support worldwide development of all new chemical entities originating from the U.S. Discovery groups. In 1991, I was transferred to SB's Great Burgh site in the U.K., where I assumed the position of Director of Pharmaceutical Development. As Director, I was responsible for formulation development and analytical method development as well as clinical trial supply testing for new chemical entities originating from U.K. Discovery groups. In 1997, I became the Director of Pharmaceutical Development at SB's Upper Merion site. Currently, I am the Director of NCE Cardiovascular and Urogenital Product Development at Upper Merion.
2. From 1991 to 1993, while I was Director of Pharmaceutical Development at Great Burgh, I was in charge of the development of paroxetine hydrochloride formulations.

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3. On December 29, 1992, SB obtained FDA approval to market crystalline paroxetine hydrochloride in the United States. (Defendants' Exhibit (DX) 12, p. 108, Response to M.F. 387.)¹ SB planned to distribute the U.S. approved product immediately, as it did with most of its new drugs. As it turned out, however, SB was forced to delay its U.S. launch of paroxetine tablets until early 1993 due to difficulties in obtaining sufficient stock to meet the immediate and expected future market demands.
4. The insufficient tablet output resulted from the unexpected presence of a pink hue in several batches of SB's commercial scale paroxetine tablets made by wet granulation. The pink hue discoloration problem was intermittent in nature; some tableted paroxetine batches inexplicably turned an undesired pink color, while others remained white. The pink batches could not be used and thus reduced the overall number of tablets.
5. The pink hue problem was a major concern to SB for several reasons. In addition to economic and regulatory concerns, which will be discussed below, the pink hue coloration presented a major technical concern from a production standpoint.
6. The pink hue discoloration was an economic concern to SB. First, those batches of tablets exhibiting a pink discoloration fail product specifications. Producing entire batches of tablets that fail product specifications, is a significant waste of resources, time and money, and could jeopardize the commercial viability of a product.

¹ Where possible, I have cited to the exhibits relied on by TorPharm in support of its Memorandum of Law. I cite to TorPharm's exhibits as DX ____.

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7. As noted, the intermittently occurring pink hue prevented SB from producing enough tablets to meet the initial market demand. This delayed the U.S. launch of Paxil[®], resulting in the loss of millions of dollars. Furthermore, it was evident that if the pink hue problem persisted, SB might not be able to meet long-term market demand either, forcing doctors to prescribe to their patients a different anti-depressant drug that was readily and consistently available. This alone could have rendered Paxil[®] a commercial failure.
8. The intermittent pink hue discoloration was a major regulatory concern as well. The pink hue indicated potential variability in the tablet manufacturing process. If not resolved, the FDA might deem SB's tableting process "out of control" and prohibit SB from selling its paroxetine tablets entirely in the U.S. until a solution was found. Moreover, if the problem proved to be more serious, the FDA could have issued a recall of Paxil[®], destroying consumer confidence in the drug and virtually guaranteeing the commercial failure of the product.
9. Solving this problem was thus given the highest priority at SB because it related to a New Chemical Entity (NCE). An NCE is a relatively rare event at an innovator drug company such as SB, due to the years of research and tremendous capital investment required for each new product. Consequently, several working groups were formed to understand and address the pink discoloration. One such group was located at SB's Great Burgh facility, which fell under my umbrella of responsibilities as Director of Pharmaceutical Development.

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10. After an intensive investigation, it was discovered that the pink hue was caused by the formation of a red dimer referred to as the "paroxetine quinone adduct." SB determined that this dimer was produced by an oxidation reaction between paroxetine and an impurity referred to as the "paroxetine catechol." (Ex. B, at SBG02001-014103.) While it was not known at the time how the catechol got into the bulk substance, experiments performed by SB demonstrated that batches of bulk paroxetine drug substance containing higher levels of catechol produced more of the red paroxetine quinone adduct than batches containing lower initial levels of the catechol. (Ex. B, at SBG02001-014107- 014108.)
11. SB's initial response was to stop using any bulk paroxetine drug substance that contained more than 0.1% of the paroxetine catechol. (Ex. C, SBG02001-004601.) This was, however, not an entirely adequate solution, because it involved the waste of bulk drug substance. Either way, SB was wasting time, money, and resources.
12. To the surprise of everyone at SB, two members of my Research and Development Group at Great Burgh, Dr. David Doughty and Mr. Ram Pathak, found that changing SB's wet granulation tablet formulation and process to a dry admixing and compressing process significantly reduced the occurrence of the intermittent pink hue.
13. This result was highly unexpected. Water was always present in the commercial scale wet granulation process but the pink hue was only present some of the time. It was thought of course that if water were the cause of the pink hue, one would expect to see the pink hue in every batch of tablets made by wet granulation. Because this was not

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the case, no one expected that moving to a dry admixing and compressing process would have reduced the occurrence of the pink hue.

14. Dr. Doughty and Mr. Pathak also discovered that a dry admixing and compressing process could be used to make paroxetine tablets on a commercial scale. This was unexpected and contrary to SB's prior findings when they had first attempted to scale up a direct compression process. (Ex. D, SBG02001-015381.) At that time, the direct compression process was found "insufficiently robust for commercialization." In fact, it was this understanding that led SB to develop the wet granulation formulation eventually used to produce the paroxetine tablets sold in the United States. (*Id.*)
15. Dr. Doughty's and Mr. Pathak's invention was very important to SB. It allowed for the reliable and reproducible production of paroxetine tablets on a commercial scale without the need to waste either bulk drug substance or finished tablet cores because of discoloration. Hence, SB no longer wasted time, money or resources. It also resolved a potential "out of control" process before it became a major regulatory concern that could have interfered with SB's sale of its paroxetine tablets.

Dated:

Dr. Robin Roman
Dr. Robin Roman

Subscribed and sworn to me this 7 day of April, 2002

Arlene E. Cannon
Notary Public

NOTARIAL SEAL
ARLENE E. CANNON, Notary Public
Upper Merion Twp., Montgomery County
My Commission Expires May 21, 2005